Defense Threat Reduction Agency
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DTRA-TR-18-001

TECHNICAL REPORT

Modification of Acute Radiation Response in Different Demographic Age Groups

October 2017

HDTRA1-14-0003; 0005

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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

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1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
25-10-2017	Technical Report	

4. TITLE AND SUBTITLE

Modification of Acute Radiation Response in Different Demographic Age Groups

5a. CONTRACT NUMBER

HDTRA1-14-D-0003/0005

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)

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Defense Threat Reduction Agency
8725 John J. Kingman Road, Mail Stop 6201
Fort Belvoir, VA 22060-6201

10. SPONSOR/MONITOR'S ACRONYM(S)

RD-NTS

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

DTRA-TR-18-001

12. DISTRIBUTION/AVAILABILITY STATEMENT

DISTRIBUTION A. Approved for public release: distribution is unlimited.

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Accurate casualty estimation tools are critical in preparedness and response planning for nuclear and radiological scenarios. Current consequence assessment models are based on healthy adult males and may not adequately represent the entirety of an affected population. The focus of the current work was to review data on the variability in response to radiation among different ages at exposure. A significant amount of animal data was categorized by age groups corresponding to physiological and developmental stages and extrapolated to humans. Using the LD50 response in adult animals as the reference, the LD50 values from other age groups were used to obtain a dose modification factor (DMF) for non-adult age groups. The overall trend observed in the animal work was an increase in radiosensitivity among younger and older animals. The average DMF values for each category were used to extrapolate and modify the adult LD50 to estimate dose response relationships (DRRs) for different age categories in humans. The DRRs may be integrated into casualty estimation tools for population-based scenario analyses.

15. SUBJECT TERMS

Age, Demographics, Radiation Dose Response, LD50

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			Dr. Paul Blake, Ph.D.
U	U	U	U	47	19b. TELEPHONE NUMBER *(Include area code)* 703-767-3433

UNIT CONVERSION TABLE

U.S. customary units to and from international units of measurement*

U.S. Customary Units	Multiply by → / ← Divide by†		International Units
Length/Area/Volume			
inch (in)	2.54	$\times 10^{-2}$	meter (m)
foot (ft)	3.048	$\times 10^{-1}$	meter (m)
yard (yd)	9.144	$\times 10^{-1}$	meter (m)
mile (mi, international)	1.609 344	$\times 10^{3}$	meter (m)
mile (nmi, nautical, U.S.)	1.852	$\times 10^{3}$	meter (m)
barn (b)	1	$\times 10^{-28}$	square meter (m^2)
gallon (gal, U.S. liquid)	3.785 412	$\times 10^{-3}$	cubic meter (m^3)
cubic foot (ft^3)	2.831 685	$\times 10^{-2}$	cubic meter (m^3)
Mass/Density			
pound (lb)	4.535 924	$\times 10^{-1}$	kilogram (kg)
atomic mass unit (AMU)	1.660 539	$\times 10^{-27}$	kilogram (kg)
pound-mass per cubic foot ($lb\ ft^{-3}$)	1.601 846	$\times 10^{1}$	kilogram per cubic meter ($kg\ m^{-3}$)
Pound-force (lbf avoirdupois)	4.448 222		Newton (N)
Energy/Work/Power			
electron volt (eV)	1.602 177	$\times 10^{-19}$	joule (J)
erg	1	$\times 10^{-7}$	joule (J)
kiloton (kT) (TNT equivalent)	4.184	$\times 10^{12}$	joule (J)
British thermal unit (Btu) (thermochemical)	1.054 350	$\times 10^{3}$	joule (J)
foot-pound-force (ft lbf)	1.355 818		joule (J)
calorie (cal) (thermochemical)	4.184		joule (J)
Pressure			
atmosphere (atm)	1.013 250	$\times 10^{5}$	pascal (Pa)
pound force per square inch (psi)	6.984 757	$\times 10^{3}$	pascal (Pa)
Temperature			
degree Fahrenheit (°F)	[T(°F) − 32]/1.8		degree Celsius (°C)
degree Fahrenheit (°F)	[T(°F) + 459.67]/1.8		kelvin (K)
Radiation			
activity of radionuclides [curie (Ci)]	3.7	$\times 10^{10}$	per second (s^{-1}‡)
air exposure [roentgen (R)]	2.579 760	$\times 10^{-4}$	coulomb per kilogram ($C\ kg^{-1}$)
absorbed dose (rad)	1	$\times 10^{-2}$	joule per kilogram ($J\ kg^{-1}$§)
equivalent and effective dose (rem)	1	$\times 10^{-2}$	joule per kilogram ($J\ kg^{-1}$**)

*Specific details regarding the implementation of SI units may be viewed at http://www.bipm.org/en/si/.

†Multiply the U.S. customary unit by the factor to get the international unit. Divide the international unit by the factor to get the U.S. customary unit.

‡The special name for the SI unit of the activity of a radionuclide is the becquerel (Bq). ($1\ Bq = 1\ s^{-1}$).

§The special name for the SI unit of absorbed dose is the gray (Gy). ($1\ Gy = 1\ J\ kg^{-1}$).

**The special name for the SI unit of equivalent and effective dose is the sievert (Sv). ($1\ Sv = 1\ J\ kg^{-1}$).

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Acknowledgements

The authors would like to thank the experimentalists involved with collecting the data used in this report. We also gratefully acknowledge Dr. Paul Blake of DTRA/RD-NTS for programmatic support. This work was performed under DTRA contract HDTRA1-14-D-0003; 005.

Executive Summary

Accurate casualty estimation tools are critical in preparedness and response planning for nuclear and radiological scenarios. Current consequence assessment models are based on healthy adult males and may not adequately represent the entirety of an affected population. In a previous effort, human data was surveyed to identify key demographic factors that affect acute radiation response (Stricklin and Millage 2012). This work identified several demographic variables (*in utero* exposures, gender, age, comorbidity, and genetic susceptibility) which would significantly impact casualty estimates, of which age and gender would affect the largest proportion of the total population. Therefore, the focus of the current work was to collect and review both qualitative and quantitative data on the variability in response to radiation among different ages at exposure and gender. Limited data was available on gender differences in radiation response and only subtle differences in mortality was observed between males and females (Stricklin 2016). However, a significant body of literature was available on the variable mortality observed among several species of animals at different ages of exposure. Since little data in humans is available modified on acute radiation response among different age groups, a qualitative review of available human data was reviewed to support the trends observed in the animal data.

The animal data was categorized by age groups corresponding to physiological and developmental stages and these categories were used to extrapolate to expected responses in humans. Mortality data from the animal experiments were compiled and normalized within the single experiments by comparing the 50% lethality radiation doses (LD_{50}) in adult animals as compared to animals in other age groups. Using the LD_{50} response in adults as the reference, the LD_{50} values observed in other age groups were divided by the adult age group LD_{50} to obtain a dose modification factor (DMF) to represent the differential response to radiation in the non-adult age groups. Since the DMF represents relative changes in radiation response among the age groups, the use of the DMF allows us to normalize data observations among all of the animal experiments with LD_{50} values and examine the trends observed among the age groups across different experiments as well as across different species. The overall trend observed in the animal work was an increase in radiosensitivity among younger and older animals. Differences in DMFs were observed, however, the overall trends in increased radiosensitivity among young and older subpopulations were generally consistent. The average DMF values for each category were used to extrapolate and modify the adult LD_{50} to estimate dose response relationships (DRRs) for different age categories in humans. The DRRs developed from this work may be integrated into casualty estimation tools so that the potential variability in response among people of different ages within a population may be taken into account in population-based scenario analyses.

Section 1. Introduction

Casualty estimation tools that accurately predict the health risks of nuclear and radiological scenarios are critical in planning for and effectively managing potentially catastrophic events. Many currently implemented approaches in consequence assessment tools are based on data from healthy adult males and the expected health effects in this population. However, health effects from injuries and exposures vary greatly among individuals of inhomogeneous populations. Therefore, current injury estimates might significantly underestimate actual health effects when applied to the diverse population of the U.S. As such, improving casualty estimates by accounting for population variability when possible could better inform emergency preparedness planning. Further, identification of key demographic factors that affect the acute radiation response among individuals in the population will highlight vulnerable subpopulations and provide additional insight on medical response needs and treatment requirements.

A large degree of variability in response to injury has been observed in the general population, and many studies have revealed that individual response can be dictated by factors such as age, gender, genetic disposition, presence of comorbidities, and other factors. Within a given population, differences in individual responses can arise from variations in genetic polymorphisms that result in variations in immune responses, molecular repair mechanisms, or metabolism. Demographic differences that can potentially influence response to radiation injury include *in utero* exposures, age, gender, genetic susceptibility, and comorbidity factors (ICRP 1998, Streffer, Shore et al. 2003, DiCarlo, Maher et al. 2011). The results from a previously published study identified prominent demographic factors that could impact acute radiation response (Stricklin and Millage 2012). Although the study identified several factors that could significantly impact individual radiation mortality risk, the age of a person when exposed to radiation was expected to be a factor which would most significantly impact casualty estimations when estimating responses across an entire population. Therefore, this study critically examines currently available animal and human data regarding the impact of age at exposure on the acute effects of radiation exposure with an emphasis on identifying data to characterize mortality risk among different age groups. The aim of this work is to develop an understanding and methodology for accounting for the differential risks among susceptible persons within a population for the purposes of improving casualty estimations and medical resource planning.

Section 2. Purpose

The purpose of this work was to develop an approach to account for the differences in response to radiation among different age groups to support improvements in casualty estimation among inhomogeneous populations. This report documents the data available on the acute radiation response in animals at different ages of exposure to support the development of dose modification factors (DMFs) for different age categories. A brief review of the available human data for evaluation of demographic modification of radiation response was described previously (Stricklin and Pellmar 2010) and later published (Stricklin and Millage 2012). The human data are briefly summarized in this report with additional insights gleaned from recent radiation therapy studies. The qualitative evidence in humans is taken into consideration together with the available experimental data in animals to provide quantitative estimates of dose modification based on age at exposure. The DMFs developed from animal dose response data can be integrated into the Health Effects from Nuclear and Radiological Environments (HENRE) code for casualty estimation to facilitate population-based scenario analyses that account for the variability in radiation response among different age groups.

Section 3. Background

3.1 Modification of the Radiation Dose Response Relationship

The radiation dose response relationship (DRR), as measured in the LD_{50} response, is known to vary among different species. However, even within the same species, a large degree of variability has been observed (MacVittie, Farese et al. 2015). The origin of this variability stems from differences in experimental and environmental factors, as well as biological variation within a species (Crosfill, Lindop et al. 1959, Hamilton, Sacher et al. 1963, Schnarr, Dayes et al. 2007).

3.1.1. Experimental factors that impact the radiation DRR

A number of experimental and environmental factors can impact the DRR in animal experiments. The cleanliness of the laboratory environment and the quality of nutrition provided to animals can impact survival rate among experimental animals. Physical aspects of irradiation can impact the response to radiation as well. Furthermore, the quality of radiation (gamma, neutron, proton, etc.), dose rate, fractionation, and homogeneity of the exposures are all known to impact the acute radiation DRR (Broerse and Macvittie 1984, MacVittie, Farese et al. 2015). Therefore, careful attention to experimental details and, in particular, dosimetry and comparability of radiation exposures are needed to delineate actual differences in dose response. Physical and experimental details make meta-analyses and the extraction of meaningful quantitative data particularly challenging with radiation studies. However, in the current analysis, the relative shift in the observed LD_{50} values are reviewed by using the DMF from the reference adult response in each individual study. Since relative shifts are more comparable between studies, calculating DMFs provide a means to compare and potentially combined the observations across studies.

3.1.2. Demographic factors that impact the radiation DRR

A wide variability in response to radiation damage and injury is observed across the population. From epidemiological studies, a number of demographic factors are known to influence individual response to injury or insult. Such factors include age, gender, genetic disposition, health status, and other individual specific parameters. Factors such as age can influence the body's ability to handle insult due to an immature immune system that is not fully developed, an aging immune system that is compromised, or differences in other mechanisms, such as DNA repair, that can be affected by age. Gender effects can be observed in some cases due to differences in endocrine responses or other mechanisms. Some variation in individual responses within a population arises from genetic differences in immune response, molecular repair mechanisms, and metabolism. Finally, health status, in particular the existence of comorbid conditions, nutritional status, and individual factors such as smoking, alcohol consumption, and use of pharmaceuticals can all impact individual susceptibility to insult and injury.

3.2 Impact of Radiation Response Based on Age at Exposure

3.2.1. Long-term health effects

The stochastic effects of radiation exposure, in particular, the carcinogenic risks associated with radiation exposure, has been studied extensively in experimental animal studies and human populations exposed to radiation. From this body of literature, age at exposure has been shown to significantly impact the carcinogenic risks from radiation exposure, with risks increasing with decreasing age (NRC 2006). Although the impact of age on carcinogenic risks has been well-established, a comparable risk relationship for deterministic effects such as lethality with regard to age at exposure to radiation has not been well established for humans.

3.2.2. Deterministic effects: Acute mortality risk

Age at radiation exposure is a prominent source of variability in mortality risk since the age of an individual can greatly impact their ability to handle insult or injury. At very young ages, the immune system is not fully developed and can potentially result in greater risk of infection. At the same time, infants before weaning are afforded some protection from infection through the mother's milk (Simon, Hollander et al. 2015). During different developmental periods, a child's body is undergoing rapid growth which can result in greater susceptibility to radiation damage, but may also result in faster repair of damage. As individuals mature toward adulthood, increases in hormone levels could also potentially impact radiation response. The status of hormones has been shown to be associated with carcinogenic risks (NRC 2006), and hormones and growth periods may impact deterministic effects as well.

As adults age, their immune systems also begin to age resulting in a decline in immune status and the ability to repair damage (Gomez, Nomellini et al. 2008, Nomellini, Gomez et al. 2008, Fulop, Dupuis et al. 2016, Pereira and Akbar 2016). Immuno-senescence is in part associated with decreasing telomere length, but the complex interactions involved in aging are not fully understood and are currently an active area of research. In addition to the impaired immune response in aging populations, inflammatory processes are also impacted by aging, where chronic inflammation is common in the elderly (Jose, Bendickova et al. 2017) Since one of the major pathophysiological mechanisms in which radiation acts is through inflammatory processes, the increasing inflammatory dysfunction with age is likely to exacerbate radiation effects. Further, the number of hematopoietic stems cells decline during aging (Sharpless and DePinho 2007, Gazit, Weissman et al. 2008), and the functionality of the progenitor cells declines as well (Van Zant and Liang 2003). These processes work in concert as part of the complex set of aging processes which render aging persons at greater risk of injury while also impairing their ability to repair and recover after injury.

A variety of different mechanisms are associated with an individual's response to radiation, and the mechanisms that dictate radiation response change as an individual develops, matures, and ages. Currently, limited mechanistic data exits for understanding these complex processes in sufficient detail to model for the purpose of describing age-dependent dose responses after acute radiation exposure. Therefore, to develop a quantitative relationship of age and response for the purpose of improving casualty estimations, an approach to estimate the increased risk for different groups based on general age categories and observational lethality data has been applied. The results of these efforts are DMFs for age categories that can be used to estimate the differential acute lethality risks that may be observed among the general population.

Section 4. Methods

4.1 Animal Data

A detailed literature search was conducted to identify experimental studies that examined the effect of acute radiation exposure in short term survival (typically LD_{50} in 30 or 60 days, $LD_{50/30}$ or $LD_{50/60,}$ depending on species) in different age groups. Data were compiled from peer-reviewed studies and a meta-analysis was conducted. Of the twelve well-designed studies identified, data in five strains of mice were collected. Four studies in rats and one each in hamsters, beagles, and lambs were identified. Studies that collected and reported lethality data in terms of LD_{50} values among animals of different ages were used for estimating the magnitude of difference in response among age groups. The remaining data were used for qualitative supporting evidence of the differential responses among age groups. The collective data represented responses observed in over 21,000 animals.

4.2 Human Data

The literature was also reviewed to identify studies that might provide evidence of differential responses of humans to acute radiation exposures. Limited sources of such data are available. Most of the human data available to date relate to long-term health effects such as carcinogenesis of radiation exposure. Population sizes of individuals involved in accidental exposures are generally not large enough to examine differences in effects among different age groups. Limited data is available from the atomic bomb survivors of Hiroshima and Nagasaki. However, supporting evidence of the differences in responses in pediatric and elderly populations was identified in the literature.

4.3 Estimation of Dose Modification Factors

To develop numerical estimates of the change in radiation dose response for different age categories, the concept of a dose modification factor (DMF) was used. The concept has been used to describe the shift of an LD_{50} curve from different countermeasure treatments (Stone and Milas 1978, Connor and Sigdestad 1982, MacVittie, Monroy et al. 1991, Weiss 1997, Lutgens, Deutz et al. 2003, Weiss and Landauer 2009). This concept is based on an observed shift in the LD_{50} curve between a reference group and a treatment group or, in this case, different age groups. Since the current LD_{50} used in casualty estimation tools is based on the healthy adult, this age category (18-50 years) serves as the reference group. Therefore, the DMF is calculated by dividing the LD_{50} observed in younger or older aged animals by the LD_{50} observed in the reference population, healthy adults. As such, if the DMF is less than 1, the DMF reflects an increase in radiation sensitivity.

In cases where multiple animal groups were measured within a single age category, the data were averaged to determine an overall LD_{50} and subsequent DMF for that age category. The age of animals was categorized according to published data on how the age in different species relate to human age groups (Andreollo, Santos et al. 2012, Sengupta 2013, Anderson, Otto et al. 2015, Dutta and Sengupta 2016) and is presented in Table 1. The mapping of animal age groups to equivalent human ages is an approximation based on the age of weaning for infants, the period of development, growth, and sexual maturation for juveniles, reproductive maturity for adults, reproductive senescence for late adult, and post-reproductive senescence and immuno-senescence for aging or elderly.

Table 1. Time periods of selected age categories among different species.

		Age Span according to Species				
Category	Description	Human	Mouse	Rat	Hamster	Beagle
Infant	Birth to weaning	0-1 y	0-28 d	0-21 d	0-21 d	0-2 mo
Juvenile	Developing	>1-18 y	>28-70 d	>22-70 d	>21-70 d	>2-18 mo
Adult	Reproductive maturity	>18-50 y	>70-350 d	>70-510 d	>70-365 d	>1.5-8 y
Late adult	Reproductive senescence	>50-65 y	>350-540 d	>17-22 mo	>12-18 mo	>8-11 y
Elderly	Physical decline	65+ y	540+ d	23+ mo	19+ mo	12+ y

Section 5. Results

5.1 Animal Data

The data from twelve studies conducted in five different animal species were used to examine the impact of age at exposure on the acute effects of radiation response. To mathematically describe the impact of age on radiation lethality, studies that measured the dose response between different age groups provided valuable quantitative data for establishing dose modification values. Studies that reported LD_{50} values were collectively used to establish DMFs. Other studies that evaluated the impact of age on acute radiation response but that did not report LD_{50} values were also reviewed and are discussed to provide supporting evidence as in the changes observed in the selected animal studies. The studies are briefly discussed according to species.

The 30- and 60-day lethality rates and survival times were examined in C57 black mice, aged from 1 to 90 days, exposed to single acute doses of 550 cGy x-irradiation (Abrams 1951). Observed mortality rates were variable among the groups, ranging from 90% to 13.5%. Juvenile mice (aged 30-, 45, and 60-days) demonstrated 90%, 46%, and 19% mortality at 60 days, respectively. The precise phases of life for different strains of mice are difficult to map to human age groups, but the study demonstrates that in general radioresistance increases as mice approach adulthood. Relative to adult mice (90-days), the increased risk for juvenile animals with different ages at exposure can be examined in terms of an Odds Ratio as shown in Table 2. The greatest risk observed in this study was in mice 30 days old, the time period just after weaning.

Table 2. Mortality in mice according to age at exposure (Abrams 1951).

Age (days)	No. mice	30-day % mortality	60-day % mortality	OR for 60-d mortality*
1	58	22.5	60	9.9
15	57	26.5	30	2.8
30	59	90	90	57.4
45	65	46	46	5.6
60	52	19	19	1.6
90	45	13.5	13.5	1

*The Odds Ratio was calculated relative to 90-day old mice.

A series of studies which examined the LD_{50} responses in different species and ages of mice were identified. These data are collectively presented in Figure 1 and Table 3. To obtain relative changes among key age categories for each study, the LD_{50} values of ages within the same age ranges for the categories (as identified in Table 1) are averaged and presented in the last column of Table 3.

Radiation sensitivity as a function of age and gender was examined in groups of mice (400 animals per group) acutely exposed to 15 MeV x-rays (Crosfill, Lindop et al. 1959). Younger mice demonstrated increasing tolerance to radiation in age ranges up to 30–48 weeks at exposure; the radiation tolerance began to decline in mice older than 48 weeks at exposure. The observed $LD_{50/30}$

values for animals of different ages are provided in Table 3 and compared with other data collected in mice in Figure 1.

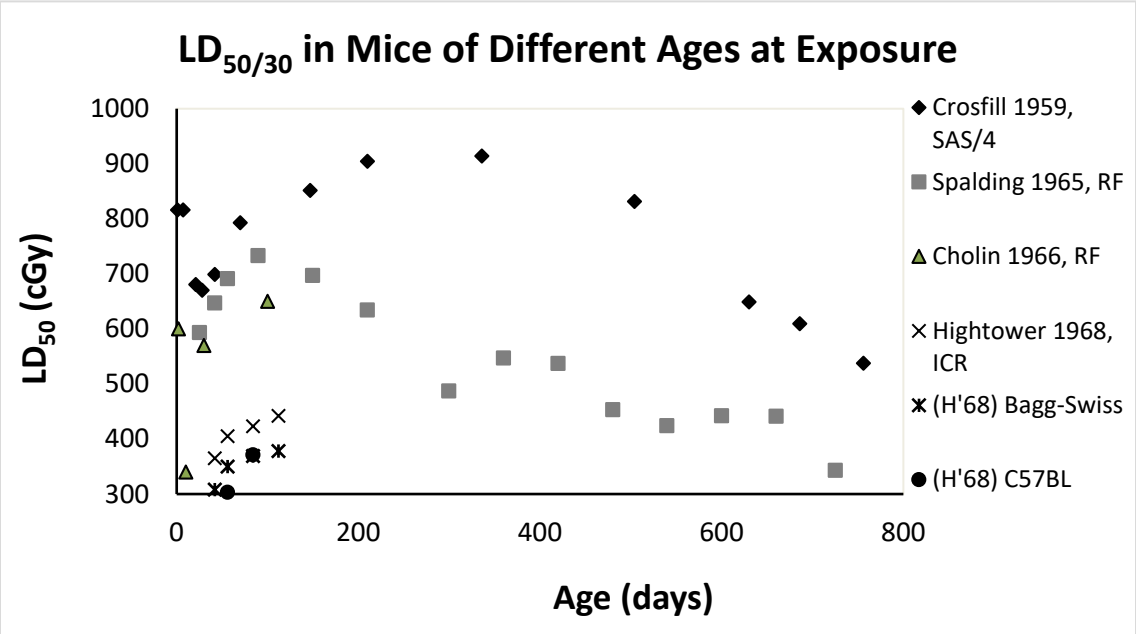

Figure 1. Trends in radiosensitivity in mice according to age at exposure.

Data later reported as part of this data set include two additional groups as noted in Table 3 that could be categorized as elderly animals, and these animals show a dramatic increase in radiosensitivity as compared to the younger groups (Lindop and Rotblat 1962). Small differences in radiation sensitivity between male and female mice were observed, but the radiosensitivity among the sexes varied depending on the age of the animals.

The $LD_{50/30}$ values from female RF mice exposed to 250 kVp x-rays were obtained from a study that included a total of 2,930 mice in 14 different age groups (Spalding, Johnson et al. 1965). The $LD_{50/30}$ values ranged from 733 cGy in young adults to 343 cGy in elderly mice. Young adult animals had the highest LD_{50} values as shown in Table 3 and Figure 1. The study shows that young mice have relatively less radiosensitivity than older mice. Infant and juvenile mice showed an increased sensitivity to radiation as compared to adult mice, likely due to their ongoing growth. Older mice had significantly higher sensitivity to radiation that continued to increase with age which is most likely due to the aging immune and repair systems that cannot adequately handle the damage incurred from radiation exposure.

Table 3. $LD_{50/30}$ values in mice according to age.

Study	No. animals	Age at Exp. (days)	Age Category	LD_{50} (cGy)	Average LD_{50} (cGy)[1]
	400	1	Infant	816±36	746

[1] Average LD_{50} for each age category defined in Table 1. Within each study, values for infants, juveniles, adults, late adult, and elderly animals are combined, and average LD_{50}s for each age category are presented.

Study	No. animals	Age at Exp. (days)	Age Category	LD_{50} (cGy)	Average LD_{50} (cGy)[1]
Variation of sensitivity to ionizing radiation with age. (Crosfill, Lindop et al. 1959) SAS/4, male and female 15 MeV x-rays 400 r/min	400	7	Infant	816±12	(670-816)
	400	21	Infant	681±12	
	400	28	Infant	670±15	
	400	42	Juvenile	699±10	746
	400	70	Juvenile	793±19	(699-793
	400	147	Adult	852±29	890
	400	210	Adult	904±12	(852-914)
	400	336	Adult	914±14	
	400	504	Late adult	831±9	831
	400	630	Elderly	649±48	599
	400	686[2]	Elderly	635	(560-649)
	400	756[2]	Elderly	560	
Acute radio-sensitivity as a function of age in mice. (Spalding, Johnson et al. 1965) RF, female 250 kVp x-rays 50 rad/min	326	25	Infant	593±14.6	593
	186	42	Juvenile	647±18.9	669
	210	56	Juvenile	691±14.8	(647-691)
	190	90	Adult	733±13.5	
	300	150	Adult	697±15.8	638
	363	210	Adult	634±20.3	(487-733)
	131	300	Adult	487±18.7	
	120	360	Late adult	547±35.9	
	157	420	Late adult	537±16	490
	125	480	Late adult	453±5.16	(360-540)
	179	540	Late adult	424±22.8	
	149	600	Elderly	442±17.6	409
	152	660	Elderly	441±12.5	(343-442)
	342	725	Elderly	343±18.6	
Peculiarities due to age in the development of acute radiation disease in mice. (Cholin 1966) RF, 180 kV, 70 R/min	380	1-3	Infant	576	451
	301	9-10	Infant	326	(326-576)
	313	30	Juvenile	547	547
	596	90-120	Adult	624	624
The effect of age, strain, and exposure intensity on the mortality response of	96[3]	42	Juvenile	365±20	385
	96	56	Juvenile	405±18	(365-405)
	96	84	Adult	423±13	433
	96	112	Adult	442±30	(423-442)

[2] Reported in Lindop, P. J. and J. Rotblat (1962). "The Age Factor in the Susceptibility of Man and Animals to Radiation " **35**(409).
[3] ICR mice

Study	No. animals	Age at Exp. (days)	Age Category	LD_{50} (cGy)	Average LD_{50} (cGy)[1]
neutron-irradiated mice. (Hightower, Woodward et al. 1968)	96[4]	42	Juvenile	308	329
	96	56	Juvenile	350	(308-350)
ICR, Bagg-Swiss, C57BL 1-9 MeV neutrons 200 rad/min	96	84	Adult	369±13	374
	96	112	Adult	378±10	(369-378)
	96[5]	56	Juvenile	303±18	303
	96	84	Adult	371±10	371

A study translated from the German literature included data in newborn (1-3 days), 9-10 day, 30-day, and sexually mature (3-4 months) RF mice that were compared to the data in rats (Cholin 1966). The study demonstrated variable radiosensitivity at younger ages, and sexually mature mice demonstrated greatest resistance to radiation lethality (Table 3 and Figure 1). The $LD_{50/30}$ values presented in this study indicated greater relative radiosensitivity in mice as compared to rats; the adult $LD_{50/30}$ in mice was 624 cGy as compared to 538 cGy in rats (Table 4).

Table 4. $LD_{50/30}$ in rats according to age at exposure.

Study	No. animals	Age (days)	Age Category	LD_{50} (cGy)	Average LD_{50} (cGy)
The lethal effect of acute x-irradiation on rats as a function of age. (Hursh and Casarett 1956) Wistar, female, 250 kVp x-rays, 18r/min	153	180	Adult	687	687
	191	480	Late adult	576	576
Peculiarities due to age in the development of acute radiation disease in mice. (Cholin 1966) RF, 180 kV, 70 R/min	380	1-3	Infant	259	259
	301	9-10	Infant	259	
	313	30	Juvenile	288	288
	596	90-120	Adult	538	538
On age-related radiation sensitivity of white rats. Determination of the $LD_{50/30}$ during infant period and growth	100	0	Infant	210	321 (210-373)
	106	2	Infant	275	
	419	4	Infant	308±35	
	402	8	Infant	316±25	
	550	12	Infant	365±27	
	261	12	Infant	358±57	

[4] Bagg-Swiss mice
[5] C57BL mice

Study	No. animals	Age (days)	Age Category	LD_{50} (cGy)	Average LD_{50} (cGy)
period. (Reincke, Goldmann et al. 1968) Wistar, male and female, 200 kV, 100 R/min	384	16	Infant	373±30	445 (365-551)
	574	20	Infant	366±21	
	734	24	Juvenile	365±37	
	383	32	Juvenile	370±16	
	394	32	Juvenile	406±16	
	180	48	Juvenile	533±28	
	167	64	Juvenile	551±19	
	192	128	Adult	540±16	522 (503-540)
	95	280	Adult	503±46	
Age at x-irradiation and acute radiation mortality in the adult male rat. (Jones, Osborn et al. 1969) Sprague-Dawley, male, 250 kVp x-rays, 29 R/min	100	90	Adult	817±16	840 (817-864)
	102	210	Adult	864±35	
	95	510	Late adult	743±27	754 (743-764)
	72	630	Late adult	764±34	
	86	720	Elderly	695±26	695

The effect of neutron irradiation on the mortality of three different strains of female mice (ICR, Bagg-Swiss, and C57BL) at different ages of exposure (6-12 weeks) and at exposure rates (1-200 cGy/min) has also been investigated (Hightower and al. 1968). Increasing dose rates resulted in an increase in $LD_{50/30}$ from 393 cGy to 435 cGy at 12 weeks of age demonstrating higher tolerance to neutrons at higher dose rates. Although this finding is interesting since the higher dose rates for gamma and x-irradiation increase mortality as a result of reduced time for repair, the information relevant to our current investigation pertains to impact of age on the response and the variation in response among the strains examined. The data shown in Table 3 and Figure 1 indicates a general trend in which adult mice are less radiosensitive than younger animals.

The radiosensitivity varies among the strains, with the C57BL mice demonstrating the greatest radiosensitivity and the ICR mice the least. The relative modification of radiation response between the ICR and Bagg-Swiss mice was very consistent; adults 16 weeks of age (112 days) had the least sensitivity to radiation. The youngest group, 6 weeks of age (42 days, juvenile) had the greatest sensitivity.

Several studies report $LD_{50/30}$ values in Wistar and Sprague-Dawley rats as a function of age. The available data has been summarized in Table 4 with the trends of radiosensitivity presented in Figure 2. The study by Hursh and Casarett focused on characterizing increased lethality observed in older rats as compared to adult rats; $LD_{50/30}$ of 687 cGy for rats at 6 months of age at exposure compared to 576 cGy for rats at 16 months of age at exposure (Hursh and Casarett 1956). As referenced previously, the Cholin study indicated that rats had greater radiosensitivity than mice, but the data presented in this work demonstrated a more consistent response of increased lethality in younger animals, which authors note is observed before the animals reach sexual maturity (Cholin 1966). An increase in radiosensitivity is observed with increasing age.

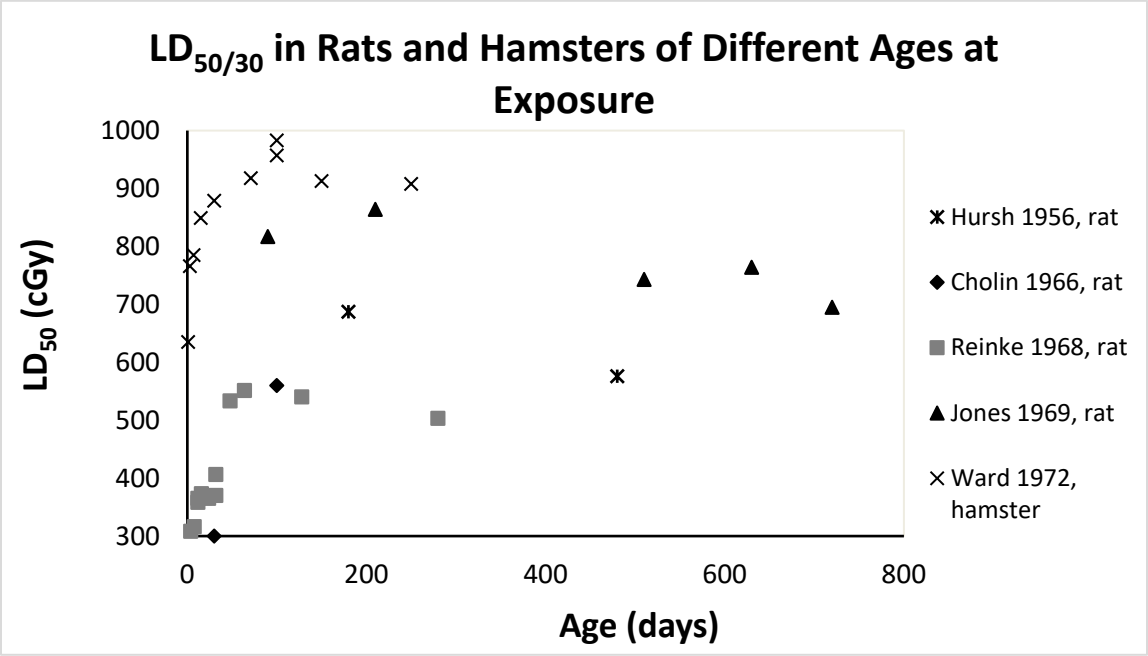

Figure 2. Trends in radiosensitivity in rats and hamsters according to age at exposure.

Reinke, et al. pooled the data from several studies on the 30-day mortality in white rats aged from birth to 280 days, representing data from a total of 4,735 animals (Reincke, Goldmann et al. 1968). The lethality response in terms of the $LD_{50/30}$ observations among rats of different ages were significantly different as shown in Table 4.

Infant rats (ages 0-20 days) demonstrated significantly greater radiation sensitivity ($LD_{50/30}$ 210-366 cGy) as compared to juvenile (24-64 days; $LD_{50/30}$ 365-551 cGy), and adult rats (128-280 days, $LD_{50/30}$ 540-503 cGy). An analysis of the slopes of probit curves in this work showed some variation among the groups; however, due to the large degree of variability observed in the data, a quantitative assessment of changes in the slopes of the probit curves was not possible.

Jones et al. investigated the lethality of 250 kVp x-rays in male rats aged 90 to 720 days (Jones, Osborn et al. 1969) which showed trends consistent with the observations by Spalding (1965). The overall magnitude of trends in radiosensitivity for different age groups is comparable and young adult rodents demonstrated less radiosensitivity than older animals. An evaluation of the probit slopes in this study revealed that most age groups were similar except for the youngest group (3 months) which demonstrated a statistically significant steeper slope. This group also demonstrated a significantly longer survival times than the older groups (16.9 days vs. 12-10.1 days).

An additional study translated from the Russian literature provided mortality data in rats as a function of age, radiation dose, and time after exposure (Kholin 1974). Predominately supra-lethal radiation exposures (2 to 500 Gy) were used; therefore, the majority of animals exposed to >10 Gy died within the first 9 days. The 30-day survival was reported for animals exposed to 2, 5, and 10 Gy. The data for newborn, 9- to 10-day old, 25- to 30-day old, and mature animals are summarized in Table 5 and show a direct correlation of increased radioresistance with increasing age in this bracket of ages.

Table 5. 30-day survival in rats according to age and radiation dose (Kholin 1974).

	Percent Survival		
Age	**2 Gy**	**5 Gy**	**10 Gy**
Newborn	91.6	2.5	0
9-10 d	91.1	2.9	0
25-30 d	92	6.3	0
Mature	100	57.8	8.2

The results of two mortality studies in Chinese hamsters of different ages exposed to single doses of 250 kVp x-rays were reviewed (Ward, Childress et al. 1972) and are presented in Table 6 along with the probit slopes for each age group. Chinese hamsters are weaned at 21-25 days, are considered sexually mature at 8-12 weeks (56-84 days), and have a lifespan of 2.5 to 3 years (Anderson, Otto et al. 2015). As such, the study shows the greatest resilience to radiation in young adult hamsters just after sexual maturity. The youngest animals had the greatest sensitivity, although increasing sensitivity was observed with increasing age past adulthood. Figure 2 shows a significant increase in sensitivity in 1-day old hamsters, a trend of increasing radiation resistance through maturation that peaks in animals of 100 days of age at exposure, and a subtle increase in sensitivity thereafter. As in most studies, large variability among the age groups was observed, and the probit slopes were not significantly different among the groups.

Table 6. $LD_{50/30}$ in Chinese hamsters of different ages (Ward, Childress et al. 1972).

Age (days)	**Category**	**No. hamsters**	**LD_{50} (cGy)**	**SD**	**Probit Slope[6]**	**SD**
1	Infant	347	635	621, 649	1.20	0.96, 1.43
3	Infant	163	766	750, 783	1.44	1.06, 1.81
7	Infant	212	785	766, 803	1.03	0.71, 1.35
15	Infant	152	849	778, 919	1.08	0.25, 2.40
30	Juvenile	228	879	863, 895	1.19	0.83, 1.45
71	Adult	116	918	907, 929	1.19	0.97, 1.41
100	Adult	218	983	962, 1010	0.84	0.55, 1.12
100	Adult	160	957	944, 971	1.70	1.25, 2.16
150	Adult	160	913	894, 932	1.25	0.93, 1.58
250	Adult	168	908	887, 930	1.00	0.72, 1.28

The 60-day mortality in beagles of different ages after acute gamma irradiation have been investigated (Garner, Phemister et al. 1974). The results from this study are presented in Figure 3. Beagles at 2 days of age at exposure had the highest $LD_{50/60}$, demonstrating the greatest resistance to radiation in this study. Similar observations were observed in a few studies in which certain infant groups, but not all infant groups, showed some level of radioresistance in the period before

[6] The probit slope units are reported per Gy.

weaning (Crosfill, Lindop et al. 1959, Cholin 1966, Ward, Childress et al. 1972). While the results are not consistent across all studies, enough evidence is available to suggest that infants may experience a short period of radioresistance, possibly corresponding to a period during which rapid growth is not ongoing and immunity is afforded from the mother's milk. In the beagle, sexual maturity is reached at about 1 year of age (Anderson, Otto et al. 2015), and as such, the young adult age group reported in this study was from 1.5 to 2 years of age. Based on the source of mortality in these animals which is attributed to the impact on the bone marrow and hematopoietic system, the authors hypothesize that the $LD_{50/60}$ is dictated by the relative bone marrow mass in animals at different stages of life.

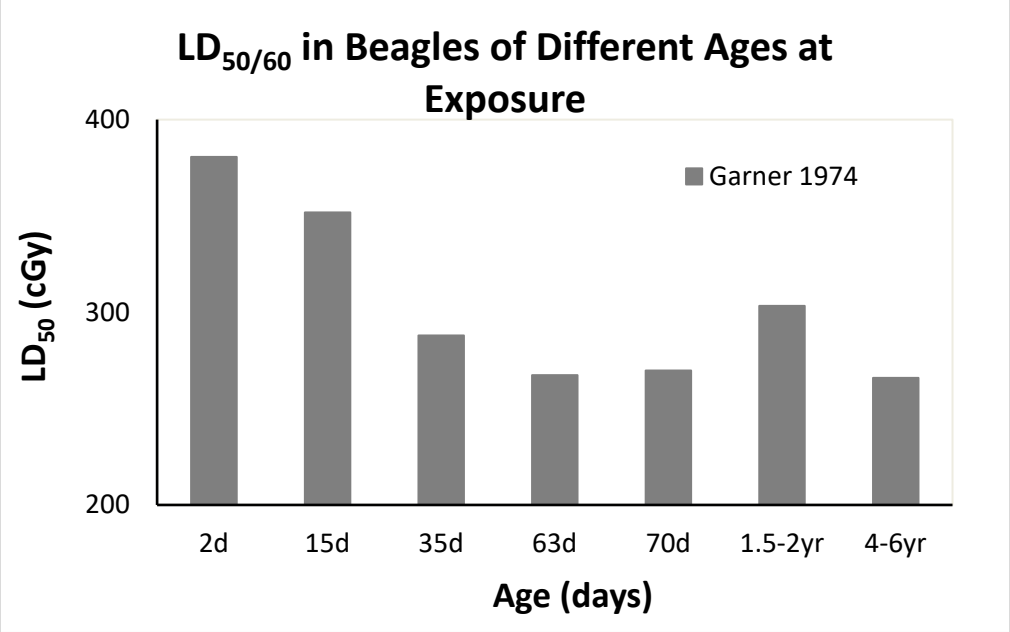

Figure 3. $LD_{50/60}$ in beagles at different ages at exposure.

For comparability to other studies, the modification is also calculated relative to adult dogs. As illustrated in Table 7, except for the 2- and 15-day old animals, young adult dogs remain the most radiosensitive. The authors do not discuss the possibility that the animals at 2 and 15 days of age have not been weaned and may have some protection from infection from their mother as a result. This study did not examine aged animals. The typical life span of beagles is 12-15 years, with 6-8 years being the end of their reproductive life span (Anderson, Otto et al. 2015).

Table 7. $LD_{50/60}$ in beagles of different ages (Garner, Phemister et al. 1974).

Age	Age category	No. dogs	LD_{50} (cGy)
55 d gest.[7]	In utero	132	298
2 d	Infant	165	381

[7] Fetal exposures at 55 days of gestation.

15 d	Infant	60	352
35 d	Infant	70	288
63 d	Juvenile	55	267
70 d	Juvenile	110	270
1.5-2 y	Adult	48	303
4-6 y	Adult	20	266

Mortality in lambs (2 to 4 days of age) exposed to ^{60}Co was investigated and compared to the reported $LD_{50/60}$ values in adult sheep (Roberts and Pfeffer 1980). The $LD_{50/60}$ in lambs was 900 cGy as compared to reported values for adults, ~300 cGy, which provides evidence indicating potential radiation resistance in young animals. However, this study did not include adult sheep; the authors compared their data in lambs to the values for adult sheep obtained in separate studies. Since study design, radiation source, dose rate, and laboratory environment can impact mortality rates in dose response experiments, the comparison of mortality in lambs and adult sheep in this paper should be considered qualitative. Further, the study included only four animals per group and mortality incidence was inconsistent with increasing radiation dose. For these reasons, the data from this study has not been included in our final assessment.

5.2 Other Supporting Animal Studies

Additional data regarding the effect of age on acute radiation mortality are available in the literature in which endpoints other than lethality dose response are measured. For example, the mean survival time in chronically irradiated (100 cGy, 5 days/week) adult and aging female mice showed that the mean survival time decreased dramatically in aging animals, from about 35 days to 5 days in the oldest animals (Sacher 1957).

The resilience of juvenile and young adult mice was demonstrated in a study that examined hematological recovery in three age groups of female mice exposed to 279 cGy (Rugh and Pardo 1963). Mice 6-8 weeks old had the least decline and fastest recovery of hematological parameters but were not dramatically different than mice older than 4 months. However, older mice (>14 months) were significantly more affected and had slower recovery with most hematological parameters not returning to normal during the 12 week study. In another study, life-shortening decreased with increasing age in mice aged 1 day to 30 weeks at exposure, in part due to the remaining life expectancy (Lindop and Rotblat 1965). A study on the effects of acute brain damage as a function of age in rats showed that 1-week old rats exposed to 5 Gy of 1000 kVp x-rays were far more affected than 52-week old animals (Diller and Brownson 1964).

The mortality in juvenile, young adult, and middle-aged beagles after injection of ^{137}CsCl has been investigated (Nikula, Muggenburg et al. 1996). Middle-aged dogs had significantly shorter survival times the juvenile or young adult animals, supporting the assertion that aging animals demonstrate greater radiosensitivity.

Other studies provided further mechanistic insight into the observed age effect of radiation responses. For example, studies in thoracic irradiation of mice showed that young animals demonstrate more acute inflammatory lung injury and decreased levels of migratory inhibition factor than adult mice (Mathew, Jacobson et al. 2013). The same factors were reportedly associated

with senescent mice in previous studies. Collectively, the evidence suggests that inflammatory pathways may play an important role in mortality, and the state of the immune system may impact age-dependent survival rates.

5.3 Human Data

5.3.1. Data from the atomic bomb survivors

Data collected by the Joint Commission for the Investigations of the Effects of the Atomic Bomb in Japan (Oughterson, LeRoy et al. 1951) provides some information on the frequency of acute radiation symptoms in different age groups. In 13,503 twenty-day survivors of the Hiroshima and Nagasaki atomic bombs, thirteen symptoms were elicited in four age groups (0-4, 5-14, 15-49, and 50 years or older) stratified by radiation exposure as determined by distance from hypocenter. No significant trends dependent on age were observed in these data; however, the majority of the persons examined were in the 15-49 year old age-group which makes reliable comparisons among age groups difficult. The numbers of persons in other age groups were too limited to observe any age-related effects. The compiled data from Hiroshima and Nagasaki in the highest exposure group for four symptoms are presented in Table 8.

Table 8. Symptoms observed in highest exposure group of twenty-day survivors of Hiroshima and Nagasaki by age

		Percent of Persons with Symptoms			
Age (years)	Total No. Persons	Epilation	Purpura	Bloody Diarrhea	Vomiting Day of Bombing
0-4	14	50.0	7.1	14.3	14.3
5-14	100	57.0	16.0	4.0	22.0
15-49	729	66.8	47.6	10.3	32.4
50+	64	34.4	37.5	10.9	21.9

Based on the symptoms recorded and the limited data available, age-related differences in health outcomes from radiation exposure cannot be ascertained from this study. Radiation illness, in particular hematopoietic syndrome, in early survivors categorized by age would be more valuable in assessing differences in acute effects based on age. Another limitation with this data is that the age groupings are not optimal. As shown in Table 8, the age range in which the data from the survivors are sorted (15-49 years) includes young adults as well as middle aged adults, and the 50+ year category spans our late adult and elderly categories (see Table 1). Any differences in symptoms observed in this data could be masked due to the averaging across categories in which we expect to see differences based on our observations in animal models. From an epidemiological perspective, the data does not account for overall mortality and the most affected individuals may not show up in the 20-day survivor data available in this compendium. The full data on the population affected, resulting mortality, demographic information, and estimated radiation doses would be needed to fully evaluate this cohort. To date, a comprehensive set of data has not been identified; however, data may be available in an archive that is yet to be identified. Finally, an

issue with extrapolating observations observed in the Japanese survivors is that the population was considered to be a select population with a lower incidence of comorbidities that is found in most modern day populations.

5.3.2. Experience from radiation therapy

Although not directly correlated to immediate casualty estimates, information regarding human effects from radiation can also be gained by studying patients undergoing radiation therapy treatment for cancerous tumors. Unlike diagnostic radiology imaging procedures associated with small radiation doses from internal isotopes and external radiation sources, radiation therapy doses are much higher and can approach the thresholds where acute radiation effects are observed. Since radiation modalities used in therapy are unlike that experienced in emergency response situations in which the affected population will receive whole-body mixed-field radiation, information gleaned from therapy can only serve as a qualitative information regarding any age-dependent differences in response. Radiation therapy treatments are localized, highly targeted, to a cancerous tumor region. Treatment doses can also be fractionated with prescribed time intervals between doses. Some treatments are designed to deliver a large amount of radiation in a single fraction and in limited cases to the whole body versus a targeted location. In general, the goals of radiation therapy are to treat the tumor with enough radiation dose to either kill the tumor or slow the growth while sparing the non-cancerous tissue which may be surrounding the tumor.

Ultimately, radiation is of concern in the human body because energy is deposited in the tissue. Acute radiation effects can be experienced following a high enough dose via any of the different types of radiation; x-rays/photons, gamma, alpha, beta, protons, electrons, and neutrons. Photons and electrons are most widely used for external beam therapy although protons (relative biological effectiveness of 1.1-1.2) are becoming popular for use in medicine to treat cancers because of their higher linear energy transfer. Proton therapy is especially good for treating tumors that are adjacent to healthy normal critical organs because when used for treatment, protons deposit the majority of their energy at the end of their path through the tissue unlike the other radiation types (Girdhani, Sachs et al. 2013).

Medical use of radiation in humans is limited in studying mortality associated with acute doses. However, the literature was surveyed to gain insight on the differences observed among age groups with regard to complications, acute radiotoxicity, prognoses, or other near-term outcomes. For example, nausea and vomiting (Schiller, Specht et al. 2017) and fatigue (Feng, Wolff et al. 2017) are acute effects of radiation therapy. These effects can be debilitating but are reversible over time. A summary of the findings relevant to the acute effects of radiation among different age groups undergoing radiation therapy are provided in Table 9.

Table 9. Studies that provide insight on the effect of age on radiation therapy outcomes.

Study	Design/Population	Endpoints	Results/Findings
Pediatric			
Radiation-related treatment effects across the age spectrum: Differences and similarities or What the old and young can learn from each other (Krasin, Constine et al. 2010)	Adults and children.	Review comparing general differences in treatment effects in both children and adults.	Radiation related effects in children and adults limit the delivery of effective radiation doses and result in long-term morbidity affecting function
Sources, effects, and risks of ionizing radiation. (UNSCEAR 2013)	Children/ adolescents	Review analyzing data, results, and literature of radiation effects in the pediatric population.	For a given radiation dose, children are generally at more risk of radiation health effects than are adults.
Adults			
Correlation between delivered radiation doses to the brainstem or vestibular organ and nausea & vomiting toxicity in patients with head and neck cancers – an observational clinical trial (Schiller, Specht et al. 2017)	26 patients receiving NSCLC to the brainstem and vestibular system	Nausea and vomiting. 65.4% experienced nausea and vomiting at least once during treatment.	Females and **younger aged patients were more prone to nausea and vomiting**.
Influence of age, prior abdominal surgery, fraction size, and dose on complications after radiation therapy for squamous cell cancer of the uterine cervix. (Lanciano, Martz et al. 1992)	1558 patients were reviewed, with a median follow-up of 43 months.	Analysis of complications in regards to treatment by radiotherapy.	A younger age (under 40 years old as compared to those over 40) were associated with an increase in complications from radiotherapy.
Elderly			
Radiation-induced organizing pneumonia after stereotactic body	78 patients (47 males with median age of 80 years old), median follow-up of 23 months,	Organizing pneumonia (OP) following stereotactic body radiotherapy.	6.4% developed OP at 6-18 months after SBRT. 8.2% at one and two years respectively.

Study	Design/Population	Endpoints	Results/Findings
radiotherapy for lung tumor (Ochiai, Nomoto et al. 2015)	treatment was stereotactic body radiotherapy (SBRT)		Radiation-induced organizing **pneumonia was observed in this elderly population**.
Comorbidity assessment and radiotherapy in elderly cancer patients (Fiorica, Stefanelli et al. 2012)	Review of findings from the treatment of elderly patients with non-small cell lung cancer, rectal cancer, breast, and prostate cancer	Comparison of geriatric index of comorbidity [GIC], adult comorbidity evaluation-27 [ACE-27], cumulative illness rating scale for geriatrics [CIRS-G] and the Charlson index, cumulative illness rating scale	Patients without or with mild comorbidities had a significantly better survival than patients with moderate/severe comorbidities. Increasing severity of **comorbidities may shorten life expectancy and increase acute toxicity.**
Stereotactic body radiotherapy for very elderly patients with stage I non-small cell lung cancer (Hayashi, Tanaka et al. 2014)	81 patients (elderly; median age, 80 years; age range 64–93 years) with stage 1 non-small cell lung cancer	Data from stereotactic body radiotherapy and its effects on elderly populations	Radiotherapy was well tolerated, feasible, and efficacious in elderly patients, however, elderly patients did experience **significantly more severe radiation pneumonitis**.
Greater influence of age than comorbidity on primary treatment and complications of prostate cancer patients: an in-depth population-based study (Lanciano, Martz et al. 1992)	Random sample of 505 prostate cancer patients	Data comparing patients with and without comorbidities on prostate cancer outcomes.	Prostate cancer patients with comorbidity did not suffer from more complications but had a **worse prognosis**.
Symptomatic radiation pneumonitis in elderly patients receiving thoracic irradiation (Kharofa and Gore 2013)	There were 99 patients > age 70 and 157 patients age < 70 years old.	Data on incidence of pneumonitis after radiation therapy.	Elderly patients were observed to have an increased risk of symptomatic pneumonitis.
Age has no impact on acute and late toxicity of curative thoracic radiotherapy (Pignon, Gregor et al. 1998)	1208 patients in 6 age ranges from 50-70 years	Data on acute and late toxicities	Age has no impact on acute and late toxicity of curative thoracic radiotherapy. No correlation of age with acute nausea and weakness; **increased weight loss**

Study	Design/Population	Endpoints	Results/Findings
			was associated with increased age.
Radiation therapy alone in elderly with early stage non-small cell lung cancer (San Jose, Arnaiz et al. 2006)	33 patients RT, aged 71–97 years.	Data on radiotherapy and acute/ late high-grade toxicity.	Radiotherapy alone was effective and low toxic in elderly with early stage NSCLC. No significant RT-related complications; incidence of both acute and late high-grade toxicity was low and similar among all age groups.

The United Nations Scientific Council on the Effect of Atomic Radiation (UNSCEAR) recently conducted a comprehensive review of the data pertaining to the effects of radiation in children, with an emphasis on the knowledge gained from radiation therapy in pediatric populations (UNSCEAR 2013). The Committee identified several factors which impact radiation effects in children: size and shape of organs, growth patterns, absorption and metabolism, hormone and endocrine changes, and physical activity. When evaluating organ and tissues specific responses, both increased and decreased radiosensitivity was observed as compared to adult responses, depending on the specific tissues under evaluation and specific time period of development. With regard to acute deterministic effects of radiation in children, higher risks were observed in organ tissues such as the brain, heart, bladder, and in the gastrointestinal tract for children over three years of age (Goldsby, Chen et al. 2011). However, effects in the bone marrow are roughly the same, and decreased effects were observed in pulmonary effects in children (Venkatramani, Kamath et al. 2013). The UNSCEAR Committee generally recognizes an increased risk from acute effects in children, but acknowledges that a complex set of factors dictate the precise response of the pediatric population to radiation.

Elderly adults are a vulnerable population to both short-term acute effects and longer term effects. Ochiai et al. (Ochiai, Nomoto et al. 2015) studied 78 patients with a median age of 80 years for the occurrence of radiation-induced organizing pneumonia following stereotactic radiotherapy for lung cancer and observed organizing pneumonia in 6.4% of the patients between 6 – 18 months following treatment. Similarly, Hayashi et al. (Hayashi, Tanaka et al. 2014) found an occurrence of radiation pneumonitis following the treatment of Stage I non-small cell lung cancer. Aging adult and elderly populations have more comorbidities than the pediatric population, and comorbidities can increase the impact of radiation damage. Chronic disease comorbidities have been found to shorten life expectancy and increase the acute toxicity associated with radiotherapy (Fiorica, Stefanelli et al. 2012). Houterman et al. (Houterman, Janssen-Heijnen et al. 2006) observed 505 prostate cancer patients and found that comorbidities were indirectly related to prognosis and did not contribute to an increase in suffering.

5.3.3. Insight from acute injury

Age is known to play a significant role in the outcome of individuals after acute injury (Smith, Cairns et al. 1994, Hollis, Lecky et al. 2006, Miller, Bessey et al. 2006, Ottochian, Salim et al. 2009, Pham, Kramer et al. 2009) and can provide additional insight in mortality after acute injury. Information on age-dependent outcomes from the acute injury community is available from a wealth of data collected by the National Burn Repository (American Burn Association) and the TRACS registry (Trauma Registry of the American College of Surgeon). In the acute injury community, a significant increased risk for mortality and morbidity is observed in the elderly age groups for both trauma and burn. However, the observed increased risk is highly correlated with comorbidity factors, such as cardiovascular disease and impaired respiratory function that can develop as a person ages (Zilberberg and Epstein 1998, Hollis, Lecky et al. 2006). Such associations are consistent with the finding from the review of age-related outcomes in radiotherapy. Nevertheless, aging in general, without regard to comorbidities, is associated with decreased survival in burn, trauma and sepsis presumably due to the decline in immune function in the elderly (Gomez, Boehmer et al. 2005, Gomez, Nomellini et al. 2008, Nomellini, Gomez et

al. 2008). The most distinct increase in mortality due to age was observed in the mild to moderate injury categories (Pham, Kramer et al. 2009).

5.4 Estimation of Dose Modification by Age

The dose response to acute radiation exposure is complex in nature and is dictated by many physical and biological parameters (UNSCEAR 1982, UNSCEAR 2001, UNSCEAR 2008, UNSCEAR 2013, MacVittie, Farese et al. 2015). However, for the purposes of casualty estimation, we propose the use of DMFs to account for demographic variance among different age categories based on the observed shifts in LD_{50} in animals and as supported by the limited evidence available in humans. The DMF concept has been used to describe the shift of an LD_{50} curve from different countermeasure treatments (Stone and Milas 1978, Connor and Sigdestad 1982, MacVittie, Monroy et al. 1991, Weiss 1997, Lutgens, Deutz et al. 2003, Weiss and Landauer 2009). Since many animal studies have reported their results in terms of the LD_{50}, the DMF concept potentially provides a convenient way to extrapolate anticipated modifications for implementation into casualty estimation codes. While some experimental and epidemiological data exists in terms of Odds Ratios, or Excess Relative Risk, insufficient human data is available for developing these values in terms of acute mortality risk per unit radiation dose. Therefore, an analysis of compiled animal data, grouped according to key age categories and normalized by determining the DMF observed within each study, has been conducted.

The data were grouped into five age groups corresponding to relevant biological and physiological life stages. Although spanning only a short time period, the data on infants were evaluated separately from juvenile children. During this period, the child is still dependent on its mother for nutrition and may be afforded some immunological protection from the mother's milk. The juvenile timeframe is an extended period of growth and development in which immunological and sexual maturation occur. Since the young are actively growing, children have significant ability to repair and recover from injury. However, tissues undergoing rapid turnover or growth can result increased sensitivity to damage from acute radiation. During the adult phase, when sexual maturation and growth are complete, the body is expected to be at its most radioresistant state. As aging ensues and reproductive senescence begins, immunological and repair functions begin to decline and characterize a late adult or middle-aged group. Further aging will result in increased frailty and inability to recover from injury (Jacobs 2003); therefore, the elderly group constitutes the final age category.

The overall DMFs observed for each age category for the studies in which LD_{50} values were published are shown in Table 10. The purpose of the DMFs are to estimate changes to the LD_{50} value used in current casualty estimations, which is based on healthy adults. Therefore, the LD_{50} responses in adult age category (18-50 years of age) are used as the reference. Subsequently, the DMFs for all of the adult animals are equal to one. As shown in these data, the overall effect in infants is an increased risk of mortality (DMF = 0.80) that decreases as animals move into juvenile ages (DMF = 0.86). As noted previously, certain narrow time frames during infancy appear to have significant radioresistance. However, translating this narrow window of resistance into a time period in humans and identifying the number of infants in which this applies to is not realistic. For the purposes of understanding population effects, the average responses observed within groups provide sufficient improvement in the estimates of the radiation mortality in a population.

The estimated DMF for juveniles represents an overall or average effect for the age range. The changes in mortality in juvenile animals varied between species and specific ages within the extended juvenile developmental period. As further noted in the review of human data (UNSCEAR 2013), the effects on radiation are tissue specific and are dictated by growth and hormone status, both of which vary during the juvenile period and among individuals. Tissues undergoing growth, in which cells are undergoing greater numbers of cell divisions, are more radiosensitive. Although the mechanisms are not completely understood, increased hormone levels are generally associated with greater effects from radiation damage. Based on the overall animal data and mechanistic bases in humans, sufficient data exists to indicate that an overall increased radiation sensitivity may be observed in children which decreases with the onset of adulthood. The broad, complex variation in response during the juvenile period is captured as a single DMF. Since the variation in radiation response is collectively a sum of the impact of many factors as noted previously (ex. growth, hormone levels, immunological development), a more detailed estimate of radiation effects within this age range would not improve the quantitative certainty of the estimated effect.

Once growth and sexual maturity are reached, the radiation response appears to be steady until aging begins and radiation sensitivity slowly increases. In this study, a moderate increase in the late adult age range (DMF = 0.86) and a more dramatic increase in mortality is expected in aged or elderly populations (DMF = 0.71) due to a natural decline in immune and repair functions. The increased mortality observed late adult animals may not be as substantial as would be observed in the typical late adult human population due to the high prevalence of comorbidities in the general population. The incidence of comorbidities increase with increasing age (Davis, Chung et al. 2011), and this increase is not observed in most laboratory animals. Comorbidities have been shown to be associated with increased complications and poorer outcomes, both in radiation therapy patients (Ludbrook, Truong et al. 2003, Modesitt and van Nagell 2005, Liu, Xia et al. 2006) and acute injury patients (Wardle 1999, McGwin, MacLennan et al. 2004, Hollis, Lecky et al. 2006, Thombs, Singh et al. 2007). Although the impact of comorbidities on radiation mortality is beyond the scope of the current work, accounting for an overall effect of age in the late adult population will help improve our estimates of mortality in the general population. However, for triage on an individual level, ascertaining the presence of one or more comorbidities may prove more useful than absolute age in making prognoses and treatment decisions.

Table 10. Radiation LD_{50} values (cGy) and dose modification factors by age category.

Study	Infant		Juvenile		Adult		Late Adult		Elderly	
	LD_{50}	**DMF**	**LD_{50}**	**DMF**	**LD_{50}**	**DMF**	**LD_{50}**	**DMF**	**LD_{50}**	**DMF**
Mouse										
Crosfill 1959	746	**0.84**	746	**0.84**	890	**1.00**	883	**0.93**	599	**0.67**
Spalding 1965	593	**0.93**	669	**1.05**	638	**1.00**	490	**0.77**	409	**0.64**
Cholin 1966	451	**0.72**	547	**0.88**	624	**1.00**				
Hightower 1968			385	**0.89**	433	**1.00**				
Hightower 1968			329	**0.88**	374	**1.00**				
Hightower 1968			303	**0.82**	371	**1.00**				
Rat										
Hursh 1956					687	**1.00**	576	**0.84**		
Cholin 1966	259	**0.48**	288	**0.54**	538	**1.00**				
Reincke 1968	321	**0.61**	445	**0.85**	522	**1.00**				
Jones 1969					840	**1.00**	753	**0.90**	695	**0.83**
Hamster										
Ward 1972	759	**0.81**	879	**0.94**	936	**1.00**				
Beagle										
Garner 1974	340	**1.19**	269	**0.94**	285	**1.00**				
Ave. DMF		**0.80**		**0.86**		**1.00**		**0.86**		**0.71**

5.5 Implementation of DMFs for Age in Casualty Estimation

The DMFs derived for different age categories can be used in casualty estimation efforts by adjusting the LD_{50} used for adults by the DMF for each respective age group. After a comprehensive review human radiation exposure data, Anno et al. proposed dose response relationships (DRR) for untreated and treated healthy adult populations based on a probit analysis of data from the Nagasaki bombing and the Chernobyl accident (Anno, Young et al. 2003). The adult LD_{50} value for a free-in-air dose without treatment was estimated to be 4.1 Gy, which is the value used in many casualty estimation tools. The form of the probit published by Anno et al. for the untreated DRR is:

Equation 1

$$p = -4.4011 + 7.133 \log_{10} D$$

where *D* is the free-in-air (FIA) radiation dose in units of Gy.

By applying the age-dependent DMFs to the adult human LD_{50} value, one can estimate LD_{50} values for each age group:

Equation 2

$$LD_{50}(age\ category) = LD_{50}(reference\ adult) \times DMF$$

The resulting LD_{50} values for each age category are as shown in Table 11.

Table 11. Proposed Human DMFs and $LD_{50/60}$ values for Selected Age Categories

Age Category	Age (years)	DMF	LD_{50} (cGy)
Infant	0-1 y	0.80	328
Juvenile	>1-18 y	0.86	353
Adult (reference)	>18-50 y	1	410
Late Adult	>50-65 y	0.86	353
Elderly	65+ y	0.71	291

Assuming the slope of the DRR probit remains constant for each age group, age-dependent DRRs can be established using the same slope of the probit function as shown in Equation 1 and the corresponding LD_{50} value to each category shown in Table 11, the DRR for the different age categories can be established as illustrated in Figure 4.

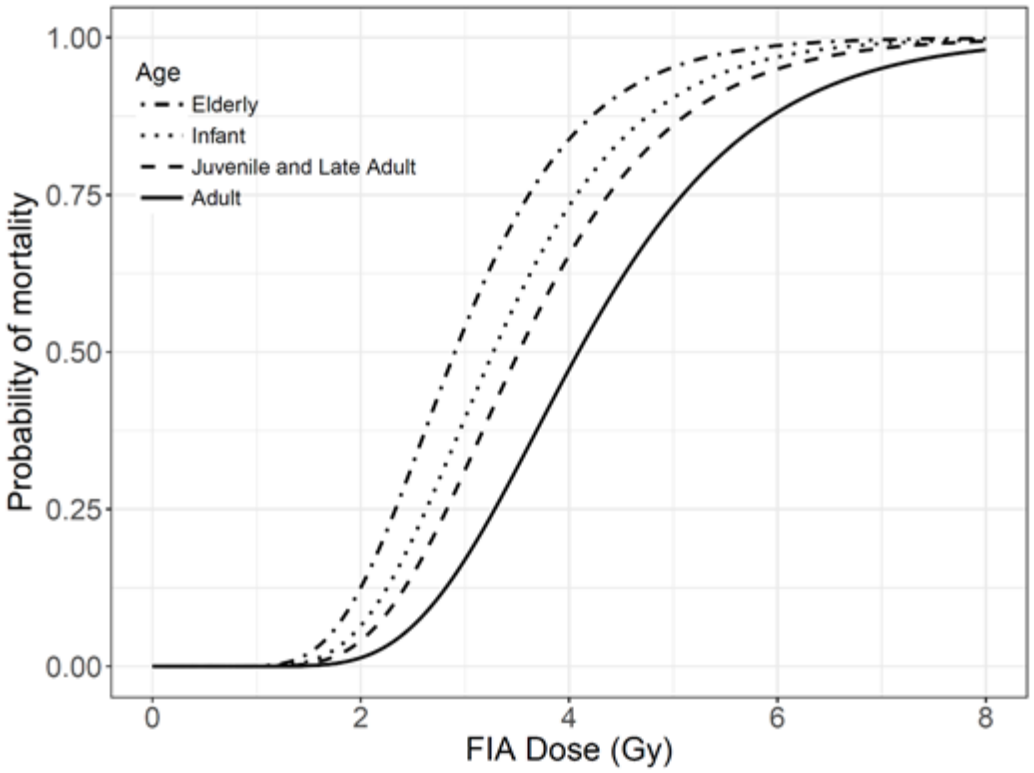

Figure 4. Proposed human age-dependent $LD_{50/60}$ curves.

These relationships can be utilized in casualty estimation tools that include age-dependent population data to provide more precise estimates of mortality in nuclear and radiological scenarios. Although the LD_{50} values provided in this work are extrapolated from animal data, they do provide a scientific basis for conducting population-based scenario analyses in which one source of population variability, age, may be examined. Since current casualty estimation tools do not account for age or comorbidities, which may increase the impact of radiation exposure, current casualty estimates may underestimate the effects of nuclear and radiological scenarios. The age-dependent dose response estimates will allow analyst to examine to what degree age-based variability might impact current estimates.

Section 6. Conclusions

Significant differences in radiation mortality are observed among different ages in animal models. However, a large number of physical, environmental, and biological factors affect radiation responses which makes it difficult to establish precise lethality curves. Nevertheless the use of DMFs provides some means to normalize data across radiation types and species to examine the trends in radiosensitivity among different age groups and provide valuable qualitative insight on the extent age may impact observed population variability. The animal and human data support increased radiosensitivity in infants, juveniles, and aging adults, with elderly populations demonstrating the greatest mortality risk from acute radiation exposure. The estimated DMFs for each age category can be used in population scenarios to improve casualty estimates by using LD_{50} curves adjusted by the DMFs for the corresponding number of people within a population in each age category. This work identifies potentially susceptible populations and provides insight on the relative degree of the increased risk that may be afforded in those populations. Furthermore, the DMFs may provide insight on how to interpret the measurements obtained from diagnostic tools which estimate radiation dose. For example, a measurement of 3 Gy may have a significantly different impact on children and elderly as compared to the effects anticipated in the average adult (see Figure 4). An improved understanding of the impact of age on acute radiation risk will allow emergency planners better prepare for radiation events and responders to better manage patients involved in such events.

Section 7. Future Work

Additional human data that includes age at exposure and observed acute effects from radiation would be greatly beneficial in validating our current modeling approach. If additional data from atomic bomb survivors becomes available, such data could be used to update or validate our current estimates of age-based dose modification. Likewise, as larger cohorts of radiation therapy data become available, age-dependent data on adverse outcomes from the acute effect of radiation treatment may also become available.

The current estimates for age-based dose modification are based on the anticipated overall response among persons in a specific age category. Except for the infant category, the age categories encompass a wide range of ages. More detailed age-dependent response may be possible to model in the future. As discussed previously, a variety mechanistic processes are known to impact age-dependent response to injury (Van Zant and Liang 2003, Sharpless and DePinho 2007, Gazit, Weissman et al. 2008, Jose, Bendickova et al. 2017). Alternate approaches to modeling age-dependent effects may become more feasible as a better understanding of how these mechanisms impact human response becomes available. In such case, a continuous estimation of the modified dose response to radiation as a function of age may be appropriate if this level of detail in casualty estimates is warranted. Regardless, mechanistic-based models will certainly facilitate a greater understanding of injury on the individual level and can serve to validate current DMF estimates.

Other prominent demographic variables to consider in population response to acute radiation exposure is the prevalence of comorbidities and genetic susceptibilities within the general population and the impact these might have on current casualty estimations. The prevalence of comorbidities with in the U.S. population is large enough to significantly impact casualty estimations. In fact, half of the U.S. population is estimated to have at least one chronic disease, and 25% of the population is estimated to have two or more chronic conditions (Ward, Schiller et al. 2014). A detailed mechanistic approach to estimating the impact of the comorbidities on radiation injuries may not be feasible. However, developing a high-level estimate of the dose modification that comorbidities would have on radiation effects would be valuable in understanding the impact of nuclear and radiological scenarios in our population.

Section 8. References

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Section 9. Abbreviations, Acronyms and Symbols

ACE-27	Adult comorbidity evaluation-27
cGy	Centigray
CIRS-G	Cumulative illness rating scale for geriatrics
CsCl	Cesium chloride
DMF	Dose modification factor
DRR	Dose response relationships
DTRA	Defense Threat Reduction Agency
ERR	Excess relative risk
GIC	Geriatric index of comorbidity
Gy	Gray
ICRP	International Commission on Radiological Protection
IMRT	Intensity-modulated radiation therapy
kV	kilovolt
kVp	Kilovoltage peak
LD_{50}	Lethal dose in 50% of the population
MeV	Mega electron volts
NBR	National Burn Repository (American Burn Association)
NSCLC	Non-small cell lung cancer
OP	Organizing pneumonia
OR	Odds ratio
R/min	Roentgen per minute
RT	Radiation therapy
SBRT	Stereotactic body radiation therapy
SD	Standard deviation